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Effects of online intervention for depression on mood and positive symptoms in schizophrenia

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Background: Depression is common in schizophrenia. Whereas the improvement of mood and self-esteem represents a subjective treatment priority for many patients, depression is rarely a primary target for clinical intervention. The present trial examined whether an online intervention for depression can ameliorate depressive symptoms in schizophrenia. **Methods:** A total of 58 individuals with schizophrenia were invited to participate in an online survey which encompassed the Center for Epidemiologic Studies-Depression Scale (CES-D, primary outcome), the Patient-Health-Questionnaire-9 (PHQ-9) and the Paranoia Checklist. Subsequently, telephone interviews were conducted to verify diagnostic status and assess symptoms (Positive and Negative Syndrome Scale, PANSS). Participants were randomized either to the experimental condition (online depression intervention) or to a waitlist control condition. Three months after inclusion, a reassessment was carried out (self-report and telephone interview blind for group condition). The trial was registered (registration: DRKS00007888).

Results: Participants in the treatment group showed a significant decline of depressive symptoms at a medium to large effect size, as assessed with the CES-D and the PANSS depression item, in comparison to the waitlist control group (completer (CC) and intention-to-treat analyses (ITT)). For the PHQ-9 (CC and ITT) and the PANSS distress subscale (CC only) significance was bordered at a medium effect size. Completion at the post-assessment after three months was 84%.

Discussion: Depression in schizophrenia is both underdiagnosed and undertreated. To reduce the large treatment gap in the disorder, low threshold strategies are urgently needed. Online treatment and bibliotherapy may represent valuable tools to address patients' needs beyond the treatment of the core positive syndrome.

1. Introduction

1.1. Depression in schizophrenia

Delusions and hallucinations (i.e., positive symptoms) are the defining features of psychosis and until recently represented the conventional target for the treatment of schizophrenia (Suzuki, 2011). In contrast, depressive symptoms in this disorder received comparatively little attention, presumably owing to historical and diagnostic reasons. Since Kraepelin (1899) who separated schizophrenia (then called dementia praecox) from affective disorders and more recently Schneider (1959) who confined the core of schizophrenia to positive features, depression is often regarded a negligible and secondary symptomatic feature of psychosis. Moreover, some phenomena that would be counted as depressive symptoms in other disorders are labeled as negative symptoms in schizophrenia (e.g., social withdrawal) or even receive distinct diagnostic terms once a diagnosis of schizophrenia has been determined (Burckhardt, 2012; Kuck et al., 1992). For example, a mental state dominated by affective numbness is usually termed melancholia in depression but anhedonia in psychosis. Similarly, lack of drive (depression) is commonly relabeled as avolition in schizophrenia and again counted as a negative symptom. This, along with the longstanding preoccupation that psychosis is not amenable to understanding (Jaspers, 1973; Walker, 1991), may have contributed to the

relative neglect of treatment of depressive symptoms in psychosis in the past and to the poor transfer of available psychological treatment options against depression in patients with psychosis.

1.2. Reasons why depression is an important treatment target in schizophrenia

A number of reasons exist why depressive symptoms deserve greater attention in the treatment of psychosis. First, beginning with Kasanin

(1933), who coined the term schizoaffective disorder, clinicians increasingly acknowledge that affective symptoms coexist with psychosis.

A review estimated that at least 50% of patients suffer from comorbid depression (Buckley et al., 2009), and many patients show single depressive symptoms such as low self-esteem (Freeman et al., 1998; Kesting and Lincoln, 2013; Moritz et al., 2010). Second, suicidality, a grave and life-threatening manifestation of depression, is frequent in psychosis and approximately 5% of patients commit suicide (Hor and Taylor, 2010). While some suicides are due to the influence of acoustic hallucinations, depression represents the best predictor for suicidality or selfharm behaviors in patients with schizophrenia (Fusar-Poli et al., 2014). Third, the implicit prevailing treatment paradigm posits that improving positive symptoms and insight will raise quality of life and reduce depression. Research suggests, however, that enhancement of insight can even paradoxically aggravate affective problems (Karow et al., 2008; Lincoln et al., 2007). Moreover, depression is not just a secondary consequence of having a severe mental disorder, it is also a frequent premorbid precursor of psychosis (Fusar-Poli et al., 2014). Fourth, depressive symptoms are often formulated by patients as their preferred target of treatment (Byrne et al., 2010; Hafner et al., 2013; Sterk et al., 2013; Moritz et al., in press-b).

1.3. Poor efficacy of available treatment

Notwithstanding the need to address depression in the therapy of psychosis as well as guidelines fostering psychotherapy in psychosis,

many patients are still deprived of psychotherapy in general (Bechdolf and Klingberg, 2014; Shafran et al., 2009). If psychotherapy is sought at all, it often targets positive symptoms. Both pharmacological and psychological treatment approaches for psychosis are only partially effective in reducing depression. Antipsychotics yield a small effect size for the improvement of depressive symptoms in schizophrenia (Leucht et al., 2009). In fact, antipsychotic medication may even induce pharmacological depression (Naber and Karow, 2001). Augmentation with antidepressants has been shown ineffective for the treatment of depressive symptoms according to two meta-analyses (Kishi et al., 2013; Kishi and Iwata, 2014), underlining the need for non-pharmacological treatment options for depression in psychosis patients. Cognitive behavioral therapy (CBT) yields a small to medium effect size (0.36) for the improvement of mood (Wykes et al., 2008).

1.4. The present study

The present study explored whether a generic online intervention for depression administered in a non-clinical setting can reduce depressive

symptoms in patients with psychosis. We used a program called HelpID (developed by the novego AG) which is based on the CBT

theoretical framework. Meta-analyses show that online interventions for depression exert a small-to-medium effect size in patients with depression when administered unguided (Cuijpers et al., 2011; Richards and Richardson, 2012; Johansson and Andersson, 2012).

Whether these effects also hold true for patients with comorbid depressive symptoms alongside other primary disorders, like obsessive-compulsive disorder, borderline personality disorder and schizophrenia, awaits to be established. While we hypothesize that

HelpID will reduce depressive symptoms in psychosis, we were unable to make predictions with respect to the magnitude of the effect. Although self-help and online interventions have proven feasible in psychosis (Alvarez-Jimenez et al., 2014), a limiting factor could be that

the online intervention under investigation is not adapted to the specific problems (e.g., stigma and self-stigma) and deficits (e.g., cognitive dysfunctions which may compromise translation of lessons/learning aims into everyday life) of psychotic patients. However, as patients with psychosis often do not receive specific treatment for depression, the potential of the program may be higher than in conventional (depression) populations who are usually not naïve about the contents of such

programs. In line with this, the magnitude of the effect of online interventions for depression was moderate for a group of neurological patients in two recent studies of whom most had never received specific treatment for depression before (Fischer et al., 2015; Schröder et al., 2014). Based on the assumption that depressive symptoms and depression-related cognitions (e.g., worry thinking style, negative beliefs about the self, interpersonal sensitivity, sleep disturbance) play a causal role for the emergence of positive symptoms (Garety et al., 2001; Freeman and Garety, 2014; Lincoln et al., 2014), we also expected the treatment to impact on positive symptoms.

2. Method

2.1. Participants

Participants were primarily recruited via a database of former patients from the Department of Psychiatry and Psychotherapy at the University Medical Center Hamburg-Eppendorf (Germany, UKE). All former patients had previously given written informed consent to be

re-contacted for future studies. While for most individuals a diagnosis of schizophrenia had been established on prior occasions, we additionally administered a diagnostic telephone interview as a precondition for participation. We also contacted high-quality Internet forums (e.g. moderated, conveying evidence-based information) devoted to schizophrenia as an additional source to recruit study participants. The following inclusion criteria applied: age between 18 and 65 years, willingness to participate in two anonymous (Internet-based) surveys as well as diagnostic telephone interviews that were scheduled three months apart, and a diagnosis of schizophrenia (as verified by telephone interview). Moreover, participants had to experience present subjective depressive symptoms and a willingness to undergo treatment for these symptoms (no formal cut-off was set). While presence of depressive symptoms was an explicit inclusion criterion, a diagnosis of major depression or dysthymic disorder was not. Severe suicidality led to exclusion. In these cases, participants were informed about help lines and treatment options. The trial was set up as an add-on intervention to care-as-usual: Participants were informed that the trial would not interfere with current treatments. For example, individuals were allowed to continue to take medication or see a physician. Interested individuals were directed to the baseline survey via a weblink. The survey was set up using questback®, a software allowing to create online surveys. The study was anonymous (no name or postal address was requested; we did not store IP addresses were stored). Participants were informed that they would either immediately receive an online code allowing a free 3-month access to HelpID or would be allocated to a waitlist control condition. The latter group was promised full access to the program subsequent to the post-assessment (online survey and interview). Group allocation was carried out in random fashion subsequent to baseline assessment (i.e. following the interview) using an automated randomization plan with no stratification. The trial was registered at the Internet Portal of the German Clinical Trials Register (DRKS; DRKS00007888). The DRKS was approved for the primary register in the WHO network and thus meets the requirements of the International Committee of Medical Journal Editors (ICMJE).

2.2. Procedure

On the first page of the baseline survey, the rationale of the study as well as exclusion criteria were summarized. All participants provided

electronic informed consent. Multiple log-ins via the same computer were prevented by means of “cookies”. The survey consisted of the following parts: demographic section (e.g., gender, age), medical history (e.g., psychiatric diagnoses), assessment of psychopathology (see

questionnaires section below), request for an email address (to match baseline and post-survey data), telephone number and contact information (e.g., preferred times for the interview) and whether prior responses had been correct. Following completion of the baseline

assessment, interviewers tried to reach individuals at their preferred times to carry out the telephone interview (the assessments are described below). Telephone interviews were conducted blinded for group allocation and patients were explicitly reminded at the reassessment not to disclose which condition they had been allocated to. Following the blinded interview (see below) eligible participants

were randomized (see above). Participants were emailed by a researcher (JS) not involved in the interviews and informed about whether they were allocated to the intervention group (a voucher providing access to the program was included along with further instructions) or the waitlist control group. Three months after the baseline interview, participants were contacted via email for participation in the post-survey. Up to two reminders were dispatched if participants failed to complete the

postassessment. For the post-survey, individuals were requested to first enter their email address to allow matching of baseline and post data. The postassessment consisted of the following parts: introduction, questionnaire on psychopathology (see below) and evaluation of the online intervention (if participants stated that they had logged in to the system at least once). At the end, participants were asked whether they had made truthful responses and were given the opportunity to leave comments (e.g., if they experienced technical problems). They were then asked for their telephone number again and for their preferred times for the final interview. Following the final blinded interview, participants in the waitlist control group received an email containing a code giving full access to the program. All participants received a relaxation manual with audio files as an additional incentive.

2.3. HelpID

The Internet intervention Help ID (developed by novego AG, Sevetal, Germany) involves 12 weekly scheduled modules, which are

derived from a pool of 17 modules (see below; 7 of these modules are mandatory). The individual set is composed according to the replies

from a pre-assessment containing 60 questions which is performed prior to starting the program. Thus, every user receives a program tailored to their individual needs. Each module requires 45 to 60 min to complete and includes 14–19 pages of text. A video moderation leads through the program, which also includes interactive exercises and practice sheets, illustrations, photographs, animations and audios. For standard use of the program, motivational SMS (optional), email reminders and personal feedback on individual questions in a protected area are provided by the psychological team. For the present study however, no personal feedback was given as we wanted to evaluate the efficacy of a fully unguided treatment program. The program is based on a combination of therapeutic methods derived from CBT, acceptance and commitment therapy (ACT) as well as systemic counseling and therapy also including relaxation audio files and music therapy, provided using an individualized algorithm considering gender-specific and symptom-related aspects, somatic variables (such as chronic back pain or cardiac arrhythmia) and potentially also postpartum depression. Additional modules on, for example, heart problems and post-partum depression were presented if corresponding cue questions (here, on diagnosed heart deficits or the birth of a child

in the last year) were affirmed. The algorithm also took into account responses on the PHQ. Essential contents and goals of the program are to convey an understanding of depression by means of psychoeducation, the development of alternative viewpoints fostering activation in everyday life, strengthening social relationships as well as attention and relapse prevention exercises. The titles of the 17 modules are as follows (modules that are underlined are mandatory and administered to every individual): the way out of depression • getting started if you have the “blues” • depression • pleasant things in everyday life • learning to reward yourself • how to break thought spirals • together against depression • recognizing yourself • relaxation against depression • attention – made easy • learning to let go • doing myself a favor • sun against murky thoughts • listen to your body • preventing relapse • therapeutic support • my heart and I. While seven of the modules were presented to each individual, five additional modules were selected according to individual responses to cue questions.

2.4. Questionnaires (online assessment)

Participants were required to complete three questionnaires. The survey proceeded only if all items had been responded to.

2.4.1. Primary outcome

The Center for Epidemiologic Studies-Depression Scale (CES-D) (Hautzinger and Brähler, 1993; Radloff, 1977) is a 20 item questionnaire covering depressive symptoms. In keeping with efforts to give patients' preferences and assessment greater consideration (Karamatskos et al., 2012), this scale represented the primary outcome of the study. The CES-D has both a good internal consistency and test-retest reliability ($r = 0.81$). Its validity has been confirmed against the Beck Depression Inventory (Beck and Steer, 1993). Items from the CES-D were mixed with those with the Paranoia Checklist.

2.4.2. Secondary outcomes

The Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001) was assessed as an additional index of depression. The PHQ-9 is a self-report instrument derived from the Primary Care Evaluation of Mental Disorders (PRIME-MD). Its nine items tap into the nine diagnostic criteria in the DSM-IV. Its psychometric properties can be judged as good with a sensitivity of 0.80 and a

specificity of 0.92 (Gilbody et al., 2007). The Paranoia Checklist (Freeman et al., 2005) consists of 18 items tapping into subclinical as well as clinical signs of paranoid beliefs and suspiciousness. The psychometric properties are good (Freeman et al., 2005; Lincoln et al., 2010). The test-retest reliability of the online version is excellent (Moritz et al., in press-a; Moritz et al., 2014) and the scale shows good internal consistency and convergent validity (Lincoln et al., 2010). In our adaption of the scale, patients were required to rate the current symptom severity on a five-point Likert scale ranging from 1 (not at all) to 5 (extremely).

2.5. Psychopathological interview

A diagnosis of schizophrenia or schizoaffective disorder was verified via telephone using the Mini-International Neuropsychiatric Interview

(M.I.N.I.; Sheehan et al., 1998). Interviewers were blind to group status (intervention or control group). The M.I.N.I. has been successfully validated against other diagnostic tools (Sheehan et al., 1998). Symptom severity was measured with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1989), which is considered the gold standard for the psychometric assessment of schizophrenia (Suzuki, 2011). The PANSS has good psychometric properties and is sensitive to change (Kay et al., 1989; Peralta and Cuesta, 1994; Santor et al., 2007). In

order to avoid repetition of questions, both ratings were synthesized into one interview and not administered successively. Ratings followed semi-structured interview protocols. Before the trial, a rater training was held using several video demonstrations. In addition, the first interview was monitored by an experienced rater (JS). The same rater administered the interview for each individual patient to avoid rating biases. For the PANSS, we adopted a five-factor algorithm suggesting

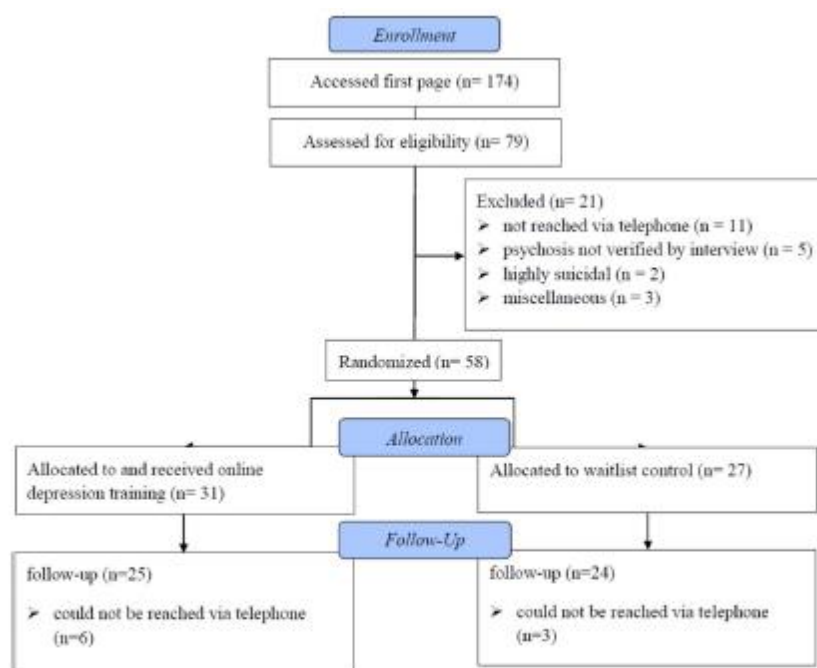


Fig. 1. CONSORT chart diagram.

the following subscales:

positive symptoms, negative symptoms, disorganization, excitement, and emotional distress (van der Gaag et al., 2006). The general item 6 (depression) served as an index for clinician-rated depression. However, as negative symptoms cannot be reliably assessed over the telephone, we did not calculate the PANSS negative subscale.

3. Results

A total of 174 participants accessed the first page of the survey; 105 participants provided their electronic informed consent. Seventy-nine

participants completed the entire baseline survey. Of these, 21 were excluded for the reasons provided in the CONSORT chart (Fig. 1). The main reason was that patients could not be reached via telephone ($n = 11$) because they either did not answer the

phone (n = 6), did not leave a telephone number at all (n = 2), or left a wrong telephone number (n=3). Thus, 58 participants fulfilling inclusion criteria were randomized to the two conditions.

3.1. Baseline characteristics & attrition

The baseline characteristics of the sample are provided in Table 1. Except for a marginal difference on age, the groups did not differ on any baseline parameter. Depressive symptoms, as assessed with the PHQ-9, were moderate to severe. The PANSS total score signaled mild/

sub-acute symptomatology for most patients. The majority of participants were on medication (HelpID: 45.5% medication only, 9% psychotherapy only, 45.5% both; waitlist control: 61.1% medication only, 0% psychotherapy only, 38.9% both, $\chi^2(1) = 2.20$, $p = 0.33$). As shown in Table 1, most individuals fulfilled diagnostic criteria for current (comorbid) depression. The rest either were diagnosed with depressive episodes in the past, dysthymia or did not fulfill formal criteria for depression. After three months, 84% of the sample (n = 49, HelpID: n = 25, waitlist: n = 24) were reached for the post-assessment (self-report and expert rating with the PANSS). Treatment status or concurrent treatment (e.g., lowered or enhanced dosage) did not change substantially between groups across time ($p > 0.1$).

3.2. Statistical analyses

In line with recommendations in the literature, we performed an ANCOVA with the pre-post difference score as the dependent variable

and the respective baseline score as the covariate. This type of analysis accounts for regression to the mean and raises power of the analyses (Borm et al., 2007; Kenward and Roger, 1997).

Table 1
Baseline characteristics. Frequency or means and standard deviations (in brackets).

	HelpID depression program (n = 31)		Waitlist (n = 27)		Statistics (t = 56)
Demographic variables					
Age in years	38.19	(11.78)	43.41	(8.42)	$t = 1.91$, $p = 0.06$
Gender (male/female)	17/14		10/17		$\chi^2(1) = 1.84$, $p = 0.17$
Years of formal school education	11.94	(1.53)	11.56	(1.45)	$t = 0.97$, $p = 0.34$
Psychopathology					
Comorbid depression	61%		64%		$\chi^2(1) = 0.61$, $p = 0.80$
PANSS total (corrected for negative symptoms)	33.39	(7.47)	35.93	(9.14)	$t = 1.16$, $p = 0.25$
CES-D	56.00	(17.26)	56.26	(16.53)	$t = 0.06$, $p = 0.95$
PHQ total	10.55	(5.66)	12.44	(6.20)	$t = 1.22$, $p = 0.23$
Paranoia checklist	36.71	(18.07)	38.41	(15.52)	$t = 0.39$, $p = 0.70$

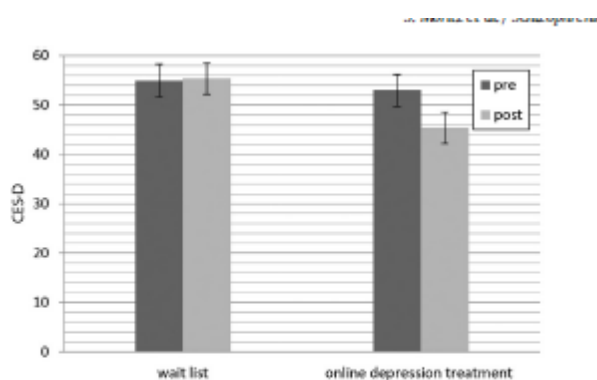


Fig. 2. CES-D: Significant decline of depressive symptoms in the intervention condition relative to the control condition with a large effect size. Bars represent standard errors.

3.3. Primary outcome (complete cases)

For the primary outcome (CES-D) a significant difference emerged, $F(1,46) = 9.84$, $p = 0.003$, $\eta^2_{\text{partial}} = 0.176$ with a large effect size in

favor of the intervention group relative to the waitlist group (see Fig. 2). Paired t-tests showed that symptoms decreased significantly in

the treatment ($p=0.002$) but not in the control condition ($p=0.822$).

3.4. Secondary outcomes (complete cases)

For the PHQ-9 a trend in favor of the treatment group emerged at a medium effect size: ANCOVA: $F(1,46)=3.71$, $p=0.06$, $\eta^2_{\text{partial}}=0.075$ (see Fig. 3). Paired t-tests showed that symptom decrease bordered on significance in the treatment ($p = 0.052$) but not in control group ($p=0.788$). As the PHQ-9 is a very short scale tapping into a heterogeneous set of symptoms, we conducted exploratory item-wise comparisons which revealed three differences in favor of the intervention group relative to the waitlist control group, particularly for self-esteem: PHQ item 6 (low self-esteem; $p = 0.003$, $\eta^2_{\text{partial}} = 0.175$), PHQ item 3 (sleep; $p = 0.052$, $\eta^2_{\text{partial}} = 0.080$) and PHQ item 7 (poor attention; $p=0.064$, $\eta^2_{\text{partial}} = 0.073$). No group differences emerged on the Paranoia Checklist across time, $F(1,46)=0.13$, $p=0.91$, $\eta^2_{\text{partial}} \leq 0.001$ (see Fig. 4). The PANSS depression item (general item 6) score decreased more strongly in the intervention group than in the waitlist control group at a medium-to-large effect size, $F(1,45) = 5.07$, $p = 0.029$, $\eta^2_{\text{partial}} = 0.101$ (see Fig. 5). We then looked at the PANSS syndrome scales, whereby a marginally significant effect emerged for the PANSS distress subscale at a medium effect size, $p=0.054$, $\eta^2_{\text{partial}} = 0.078$. For all other PANSS syndrome scores, the effects were non-significant (positive: $p= 0.986$, disorganization: $p=0.172$, excitement: $p=0.245$). Exploratory item-wise analyses revealed a significant difference in favor of HelpID for blunted affect, which however would have withstood correction for multiple testing (PANSS item N1), $F(1,46) = 5.37$, $p = 0.025$, $\eta^2_{\text{partial}} = 0.104$.

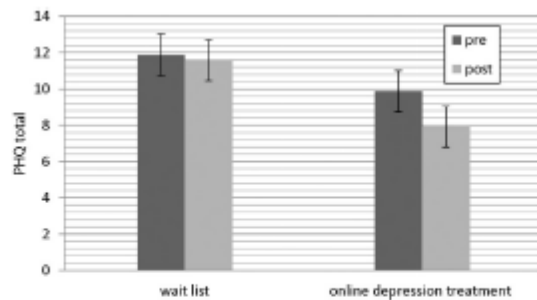


Fig. 3. PHQ-9: Decline (trend) of depressive symptoms in the intervention condition relative to the control condition with a medium effect size. Bars represent standard errors.

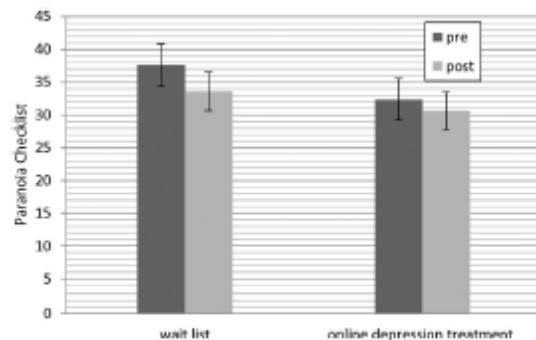


Fig. 4. Paranoia checklist: Groups did not differ across time on the decline of paranoia and suspiciousness. Bars represent standard errors.

3.5. Intention-to-treat analyses

For intention-to-treat analyses considering all randomized patients, missing outcome data were imputed from information on the psychopathological and three demographic (age, gender, school education) indexes by the expectation-maximization (EM) algorithm, trimmed to fall between the minimum and maximum of possible values. This produced largely similar findings for all variables: CES-Q ($F(1,55) = 12.023$, $p = 0.001$, $\eta^2_{\text{partial}} = 0.179$), PANSS depression ($F(1,55) = 4.356$, $p = 0.042$, $\eta^2_{\text{partial}} = 0.073$), PHQ-9 ($F(1,55) = 2.901$, $p = 0.094$, $\eta^2_{\text{partial}} = 0.05$), PANSS positive ($F(1,55) = 0.161$, $p = 0.690$, $\eta^2_{\text{partial}} = 0.003$), PANSS disorganization ($F(1,55) = 2.540$, $p = 0.117$, $\eta^2_{\text{partial}} = 0.044$), PANSS excitement ($F(1,55) = 3.218$, $p = 0.078$, $\eta^2_{\text{partial}} = 0.055$), PANSS distress ($F(1,55) = 2.591$, $p = 0.113$, η^2_{partial}

2 = 0.045), Paranoia Checklist ($F(1,55) = 0.061$, $p = 0.806$, $\eta^2_{\text{partial}} = 0.001$).

3.6. Subjective appraisal

All individuals in the HelpID condition logged in to the program at least once. Three individuals acknowledged that they did not perform

the exercises. Table 2 shows that more than almost two thirds treatment group would recommend the training to a friend, would use the

program again, found the quality of the program good and regarded the program as being helpful in dealing with problems. Endorsement

was lower for the following domains: individual help, useful for one's needs, satisfied with the degree of the help received by the program and satisfaction overall.

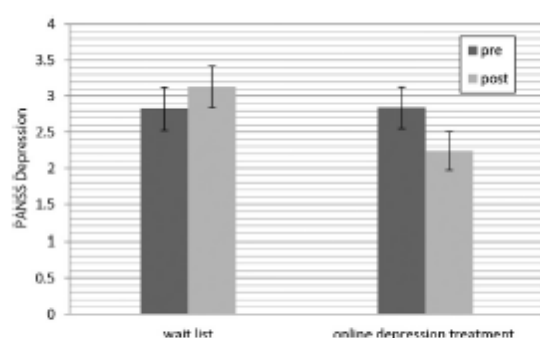


Fig. 5. PANSS depression item (g6): Significant decline of depressive symptoms in the intervention condition relative to the control condition at a medium-to-large effect size. Bars represent standard errors.

Table 2
Feedback of the group who received the HelpID depression program ($n = 25$).

Appraisal	Percentage positive versus negative appraisal
How do you assess the quality of the program? (excellent, good versus not so good, bad)	72%/28%
Did you receive the help you wanted? (yes, rather yes vs. rather no, no)	56%/44%
Did the program meet your needs? (fully applies, rather yes vs. few needs met, did not meet my needs)	56%/44%
Would you recommend the program to a friend, if she/he had needed similar help? (yes, rather yes vs. rather no, no)	64%/36%
How satisfied are you with the degree of help you received from the program (very satisfied, rather satisfied vs. somewhat dissatisfied, very dissatisfied)	56%/44%
Did the program help you to deal with problems more appropriately? (helped a lot, helped somewhat vs. it did not really help, no)	68%/32%
How satisfied are you with the program overall? (very satisfied, rather satisfied vs. somewhat dissatisfied, very dissatisfied)	60%/40%
Would you use the program again? (very much, I think so vs. I do not think so, not at all)	68%/32%

3.7. Adherence

A total of 16% of the sample used the program daily or almost daily, 28% used it once each week and 12% every two weeks. 24% used it once throughout the treatment period; 12% of the participants entered the program but did not complete any module. On average, patients logged in 28.71 times ($SD = 46.67$; range: 2–232).

3.8. Test-retest reliability

The three-month reliability was $r = 0.62$ for the PANSS total score (corrected for the negative items), $r = 0.79$ for the CES-Q, $r = 0.70$ for

the Paranoia Checklist and $r = 0.62$ for the PHQ-9.

4. Discussion

Our study examined whether a generic and unguided online selfhelp intervention for depression, leads to an improvement of depressive

symptoms in individuals with schizophrenia. Treatment of depression is of high importance in view of its prevalence in schizophrenia and because regulation of emotional problems represents a high treatment priority in patients (Byrne et al., 2010; Sterk et al., 2013; Moritz et al., in press-b). We combined the advantages of online research (e.g., economic implementation, facilitated access to patients of whom

many would not have participated in an institutional treatment context) with that of a randomized-controlled clinical trial (RCT; diagnostic

interview, external assessment with a gold-standard instrument, PANSS). We were able to recruit 58 individuals with a valid diagnosis

of schizophrenia and reached 84% of the participants after three months. The majority of participants liked the program, found it helpful, would use it again and would recommend it to others, notwithstanding that the program did not address individual problems of patients with schizophrenia. This retrospective assessment was also mirrored by the main outcome: In line with our hypothesis, we observed a significant and large decline of depressive symptoms in the HelpID group relative to the waitlist control as assessed with the CES-D. While the results pointed into a similar direction (medium effect size) for the PHQ-9, the group differences only reached trend level for this scale. An exploratory post-hoc assessment of individual PHQ-9 items revealed group differences for self-esteem (PHQ item 6). For the PANSS depression item we found a significant difference with a medium-to-large effect size in favor of HelpID. The distress subscale, which also captures anxiety, revealed a trend in favor of HelpID. No significant differences were measured for the PANSS positive syndrome or Paranoia Checklist. Thus, it seems that reducing depression does not suffice to reduce positive symptoms as assessed by this scale. However, a longer follow-up investigation is currently planned to explore whether a reduction of depressive symptoms followed by improvement on positive symptoms at a later time-point ("sleeping effect") as predicted by recent theoretical models (Freeman and Garety, 2014). Before drawing conclusions and suggesting ideas for future research, several limitations should be brought to the readers' attention. First, the sample size was rather small precluding elucidation of factors moderating outcome. Second, further follow-up studies are needed, ideally ones that include an active control condition to detect whether improvement is sustained over time. Third, unlike conventional randomized controlled trials (RCTs), it is impossible to determine the screening-to-inclusion ratio and to detect how those participating in the trial differed from those who decided against it. Thus, despite encouraging evidence for the feasibility and efficacy of the approach its effectiveness needs to be replicated in a routine setting. Finally, while assessment with the PANSS is feasible for positive and depressive symptoms via the telephone, negative symptoms are hard to verify without face-to-face contact so that we could not compute scores for the PANSS negative subscale. To conclude, the study showed that an online intervention can improve depressive symptoms in individuals with psychosis. The magnitude of the effect was larger than was expected from prior studies in patients with primary depression (Spek et al., 2007). We speculate that this is due to the naivety of the recruited individuals concerning the contents of depression treatment which permitted its full potential to unfold. In contrast, many depressed patients undergoing online interventions for depression are usually familiar with standard face-to-face therapy thereby limiting surplus effects. Of note, the effect sizes were larger than those found for conventional treatment options for depression in psychosis such as antipsychotic (small effect) and antidepressant agents (negligible effect) and CBT (small-to-medium effect). We think that the larger "dosage" of the program (e.g., weekly sessions over 12 weeks) might have augmented the effect. Future studies should investigate whether guided interventions as well as incorporating elements addressing the needs and special problems of schizophrenia patients (e.g., stigma, social withdrawal, distrust, voice-hearing) can enhance the observed effects and generalize to psychotic symptoms.

Conflict of interest

None of the authors is affiliated with Novego® enterprise who created HelpID. The Novego company was neither involved in the planning nor in analyzing the results of the trial. For the purpose of the trial, participants received free vouchers which were paid for by Novego.

Contributors

Steffen Moritz, Johanna Schröder, Jan Philipp Klein and Tania M. Lincoln designed the study and wrote the protocol. Anja Fischer and Sönke Arlt were involved in the literature searches. Steffen Moritz, Johanna Schröder and Jan Philipp Klein undertook the statistical analysis. All authors substantially contributed to and have approved the final manuscript.

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